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EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
12/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,581	KEEFE ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/30/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-12,14-20,77-85,88-94,101-114,116-127 and 130-194* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-12, 14-20, 77-85, 88-94, 101-114, 116-127, and 130-194* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/30/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment of claims 1, 9, 11, 14-16, 18, 77-85, 88-94, 101-103, 107-112, 114, and 116-127; cancellation of claims 2-4, 13, 21-76, 86-87, 95-100, 115 and 128-129; submission of new claims 133-194 in the paper filed on 09/30/2008 is acknowledged.

Claims 1, 5-12, 14-20, 77-85, 88-94, 101-114, 116-127, and 130-194 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration under 37 C.F.R. § 1.132 is Insufficient to Overcome Claim Rejections

2. Exhibit A of the declaration is objected to as the factor of the X-axis in the plot is not clearly defined. It is unknown what the numbers 200000 through to 800000 refer to. As the text of the declaration describes Exhibit A to the extent of demonstrating the yield of transcription reactions, the percentages found in Exhibit A are interpreted to be relative yields. Applicant is required to provide appropriate clarification of the given percentages. Applicant is required to provide appropriate clarification of the numbers on the X-axis.

Provided the above interpretation is sufficiently correct and further pending clarification, Exhibit A provides evidence that relative yield of the transcription reaction is

improved in the presence of both $MnCl_2$ and $MgCl_2$. However, no clear support is given and the evidence as presented is not adequate to demonstrate that the presence of both $MnCl_2$ and $MgCl_2$ is specific or unexpected with regard to transcription reactions that contain 2'-OMe NTP including 2'-OMe GTP. No comparison is given of transcription reactions that do not contain 2'-OMe NTP including transcription reactions without 2'-OMe GTP.

It is further noted that claim amendments have necessitated new grounds of rejection as given below. In the new rejections, Bishop et al. (1971) teach that transcription reactions are improved in the presence of both $MnCl_2$ and $MgCl_2$, thus making it obvious at the time of the claimed invention to use both $MnCl_2$ and $MgCl_2$ in transcription reactions.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Rejections that are Moot / Withdrawn

Canceled Claim Rejections Moot / Withdrawn

3. The rejections of canceled claims are moot and therefore are withdrawn.

Double Patenting Objection Withdrawn

4. The objection to claim 1 being a substantial duplicate of claim 101 is withdrawn as Applicant has amended the claims to differ in scope.

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

5. The rejection of claim 111 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn, as Applicant has deleted the term "substituted guanosine".

Claim Rejections Withdrawn - 35 USC § 103(a)

6. The rejection of claims 1, 5-17, 19-21, 77-96, and 101-120, 122-132 under 35 U.S.C. 103(a) as being unpatentable over by Pieken et al., Brieba et al., and Sousa et al. is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

7. The rejection of claims 18, 89, and 121 under 35 U.S.C. 103(a) as being unpatentable over Pieken et al., Brieba et al., and Sousa et al. in view of Milligan et al. is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

New Rejections Necessitated by Amendment

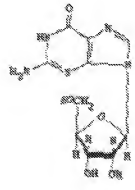
New Claim Rejections - 35 USC § 112

8. Claims 1, 5-12, 14-20, 77-85, 88-94, 101-114, 116-127, 130-194 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Independent claims 1, 101, 102, 182, and 191-194 each recite "comprises . . . 2'-OMe guanosine . . . including at least one 2'-OMe guanosine". It unclear and hence indefinite as to what limitation, if any, is intended by this recitation. Something which comprises 2'-OMe guanosine necessarily includes at least one 2'-OMe guanosine. If "comprises" is meant to include a genus of 2'-OMe guanosine it is additionally unclear what this genus is, and if the "including" is meant to include a specie of 2'-OMe guanosine it is additionally unclear what specie is intended. As the independent claims are indefinite, dependent claims 5-12, 14-20, 77-85, 88-94, 103-114, 116-127, 130-181, and 183-194 are also indefinite.

10. Dependent claims 17, 18, 89, 110, 111, 121, 138, 149, 160, and 175 are indefinite when reciting "guanosine" can be "GMP" which is guanosine mono phosphate and are indefinite when reciting "further comprises a substituted guanosine" as the antecedent base claims already recite substituted guanosines. At times the claims appear to intend "guanosine" to mean a genus and other times appear to intend for "guanosine" to be a single specie. As the metes and bounds of the claims are expressly affected by which interpretation is in effect in which claims, it is confusing and unclear as to what the claimed invention encompasses. An authority on chemical structures, Merck Index (1976) gives a single structure for guanosine as provided directly below.

4419. Guanosine



Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "guanosine" in claim 17, 18, 89, 110, 111, 121, 138, 149, 160, and 175 is used by the claims to mean "guanosine and/or monophosphate guanosine", while the accepted meaning is "guanosine." The term is indefinite because the specification does not clearly redefine the term.

Claim Interpretation

11. Owing to the indefiniteness of the claims due to claim amendments, the claims have been interpreted as follows in order to determine the applicability of the prior art. The term "2'-OMe guanosine" is indefinite as recited in the base claims and is

interpreted to be the single structure of guanosine modified with Y being OCH_3 at the 2' position as taught by Pieken et al. (1997, see the bottom left structure in Figure 1 and without the X substitution as provided for in column 1 line 25). Guanosine has been interpreted to mean guanosine as taught by Merck Index (1976).

New Claim Rejections - 35 USC § 103

12. Claims 1, 5-12, 14-17, 19-20, 77-79, 81-85, 88-94, 101-110, 112-114, 116-120, 122-127, 130-159, 161-174, and 176-194 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Pieken et al. (U.S. Patent 5,660,985 previously cited), Brieba et al. (Biochemistry (2000) 39:919-923 previously cited), Sousa et al (U.S. Patent 6,107,037 previously cited), and Bishop et al. (1971).

Pieken teaches methods of claims 1, 101, 102, 145, 148, 156, 167, 181, 182, 184, 186, and 191-194 for identifying nucleic acid ligands that bind to a target molecule (see abstract) wherein the nucleic acid ligands comprise a 2'-OMe modified nucleotide (see claim 1 and claim 10, where 2' methoxy groups are expressly claimed), (a) preparing a transcription mixture comprising a polymerase, modified dNTPs, wherein at least one NTP is 2' OMe NTP where N can be A, G, C, T or U (by teaching modified pyrimidine and purine bases can be 5-X and/or 2'-Y, here being 2'-Y only with Y being the methoxy group, see column 8 lines 38-63 and Figure 1), and specifically can be 2'-OMe guanosine (see the bottom left structure in Figure 1 and without the X substitution as provided for in column 1 line 25), magnesium and oligonucleotide transcription templates (see column 16, example 3, lines 10-1 3, where GTP, which is a

2'-OH guanosine triphosphate is used and see claim 10, which requires the use of a 2' OMe NTP),

(b) preparing a candidate mixture of single-stranded nucleic acids by transcribing the one or more oligonucleotide transcription templates including double standed templates (see Example 2) under conditions whereby the polymerase incorporates at least one of the one or more 2' O-methyl modified NTPs into nucleic acid molecules of said candidate mixture (see column 16, lines 13-35, where the T7 RNA polymerase is used to incorporate the NTPs and see claim 10, where the modified nucleotides are 2' O-methyl modified NTPs),

(c) contacting the candidate mixture with said target molecule (see column 16, example 3, lines 13-35 and claim 1),

(d) partitioning the nucleic acids having an increased affinity to the target molecule relative to the candidate mixture from the remainder of the candidate mixture (see column 16, example 3, lines 13-35 and claim 1),

(e) amplifying the increased affinity nucleic acids, in vitro, to yield a ligand enriched mixture of nucleic acids, whereby nucleic acid ligands of the target molecule are identified (see column 16, example 3, lines 13-35 and claim 1).

Further regarding claims 1, 101, 102, and 182 and with regard to claims 17, 110, 111, 130-132, 137, 159, 174, and 191-193 Pieken teaches the use of 2' OH-guanosine which is a substituted guanosine (see column 16, example 3, lines 10-13, where GTP, which is a 2'-OH guanosine triphosphate is used).

With regard to claims 9-11, 90, 91, 107, 108, 109, 122, 123, 124, 139, 140, 150, 151, 161, 162, 168, 169, and 170, Pieken teaches a purine leader sequence which is 6 nucleotides in length (see SEQ ID NO: 3).

With regard to claims 19-20, 85, 94, 112-113, 127, 143, 154, 165, 176, and 177 Pieken teaches the use of PEG (see column 15, line 49).

With regard to claims 77, 83, 92, 116-119, 125, 141, 152, 163, and 178, Pieken teaches a variety of ratios and mixtures of modified to unmodified nucleotides (see column 13, lines 5-7).

With regard to claims 78, 84, 93, 126, 142, 153, 164, and 179, Pieken teaches the transcription mixture can further comprise spermidine (see Example 2).

With regard to claims 81, 82, 90, 91, 107-109, 122-124, Pieken teaches a purine leader sequence which is 6 nucleotides in length (see SEQ ID NO: 3).

With regard to claims 188 and 190, Pieken teaches repeating the claim steps (see claim 1).

Regarding claims 1, 101, 102, and 182, Pieken does not specifically teach the use of modified polymerase and does not teach the use of Y639F or H784A T7 RNA polymerase. Pieken does not specifically teach the use of manganese.

Regarding claims 1, 5-8, 101-106, 115-119, 134, 135, 146, 157, and 182 Brieba teaches that T7 polymerase mutants at position 784 preferentially utilize 2'-OH groups

(see abstract) and position 639 mutants rapidly incorporate 2' modified nucleotides (see page 920). Brieba does not specifically teach the use of manganese.

Regarding claims 1, 14-16, 101, 102, 116-119, 133, 144, 155, 166, 171-173, 180, 182, 183, 185, 187, and 188, Sousa teaches the use of manganese and magnesium (see column 15, lines 44-48).

Regarding claims 12, 79, 88, 114, 120, 136, 147, and 158, Sousa teaches: "Preferably, the reactions also contain inorganic pyrophosphatase, which is known to increase the yields in *in vitro* transcription reactions" (see column 12 lines 41-43).

Regarding claims 1, 14-16, 101, 102, 116-119, 133, 144, 155, 166, 171-173, 180, 182, 183, 185, 187, and 188, Bishop et al. teach the use of combined manganese and magnesium for optimum performance of RNA polymerases in transcription by teaching: "The optimal conditions for assaying influenza (WSN) virion [ribonucleic acid] polymerase have been determined. The enzyme is maximally active . . . in reactions containing . . . 1 to 2 mm $MnCl_2$, . . . 8 to 10 mm $MgCl_2$, and the four ribonucleoside triphosphates at levels above certain delineated threshold values" (entire article, especially the first two sentences under the Discussion section on p. 69 and Figures 2 and 3) and by teaching in vitro synthesis/transcription with RNA polymerase (see Title, Abstract, and first sentence on p. 66). Furthermore, Bishop et al. teach concentration ratios of magnesium ions to manganese ions of 4 to 10 (8 mm $MgCl_2$ / 2 mm $MnCl_2$, = 4

and 10 mm $MgCl_2$ / 1 mm $MnCl_2$, = 10) which overlaps the claimed concentration ratios of magnesium ions to manganese ions of about 3 to 5.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the T7 RNA polymerase mutants of Brieba in the method of Pieken since Brieba notes that the polymerase with the double mutant is more likely to incorporate 2' substituents (see abstract) and since Pieken would be motivated by this teaching to utilize polymerases with superior properties for incorporation of the desired 2' modified nucleotides.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the magnesium/manganese buffers of Sousa and Bishop et al. in the methods of Pieken and Brieba. Sousa teaches regarding the use of manganese that "In Mn buffer both the w.t. enzyme and Y639F show a reduction in their sensitivity to substitution of dNTPs for rNTPs, consistent with an expectation of reduced substrate discrimination in Mn buffer (see column 22, lines 34-37)" and to use: ". . . inorganic pyrophosphatase . . . to increase the yields in in vitro transcription reactions" (see column 12 lines 41-43); and Bishop et al. teach the combined use of magnesium and manganese ions within the claimed ratio range to achieve optimum performance of in vitro transcription by RNA polymerases. An ordinary practitioner would have been motivated to use manganese buffer in optimized concentrations in order to permit incorporation of the modified nucleotides expressly desired by Pieken and Brieba. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

13. Claims 18, 80, 89, 111, 121, 138, 149, 160, and 175 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pieken et al. (U.S. Patent 5,660,985), Brieba et al. (2000), Sousa et al (U.S. Patent 6,107,037) and Bishop et al. (1971) in view of Milligan et al. (Methods Enzymol. (1989) previously cited).

Pieken, Brieba, Sousa, and Bishop teach as noted above.

Pieken, Brieba, Sousa, and Bishop do not teach the use of GMP in T7 RNA polymerase reactions.

Milligan teaches that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use GMP as taught by Milligan when performing the SELEX method of Pieken, Brieba, Sousa, and Bishop using modified GTP such as 2'-0 methyl GTP since Milligan states that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)." An ordinary practitioner would have been motivated to add GMP whenever low GTP amounts or modified GTP is being used in transcription reactions, in order to ensure the ability of the T7 RNA polymerase enzyme to prime the extension reaction.

Conclusion

14. No claim is free of the prior art.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
December 6, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637